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Remote Stereocontrol using Rotationally Restricted Amides: (1,5)-Asymmetric Induction

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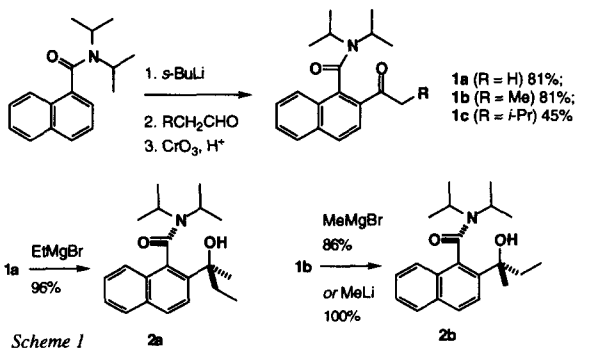
Abstract: The stereochemical influence of a rotationally restricted amide group extends widely across substituted aromatic amides. Stereogenic centres can be created with high levels of (1,5)-stereocontrol when electrophiles are added to the enolates of 2-ketonaphthamides or to lithiated 2-alkylnaphthamides. Sequential double lateral lithiation of 2,6-dialkylbenzamides can lead to compounds containing (1,5) related stereogenic centres by a process of two-directional asymmetric induction.

Compounds which are chiral because of restricted rotation have proved to be powerful tools for stereoselective synthesis.[1,2] Chiral biaryls such as BINAP and BINOL are important ligands in asymmetric metal-catalysed processes,[3] and chiral non-biaryl atropisomers are being developed for use as chiral auxiliaries.[4-6] Stereocontrol reaching over more than four atoms is rare in any system,[7-11] though one of the few effective sources of (1,6)-asymmetric induction is a BINOL derivative.[8]

The stereogenic axis (the aryl–carbonyl bond) of rotationally restricted tertiary naphthamides can act as a source of (1,4)-asymmetric induction in reactions such as additions of aryllithiums[12,13] or benzyllithiums[14,15] to electrophiles, the addition of nucleophiles to aldehydes and the reduction of ketones.[16] We now report that the stereocontrolling influence of a rotationally restricted amide group is remarkably far-reaching, and in this Letter we describe its use in the synthesis of molecules with essentially complete remote (1,5) relative stereocontrol.



Scheme 1

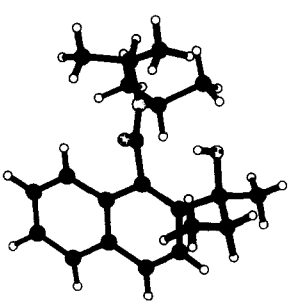
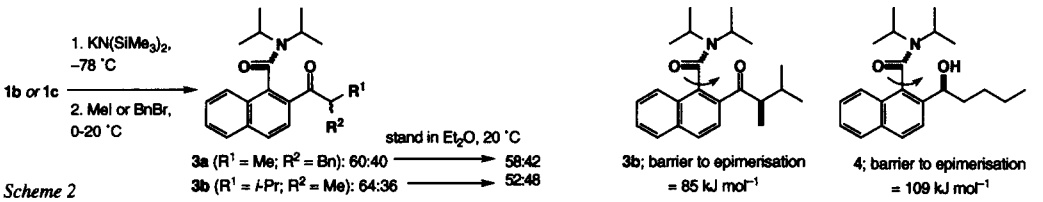


Fig. 1: X-ray crystal structure of **2a**

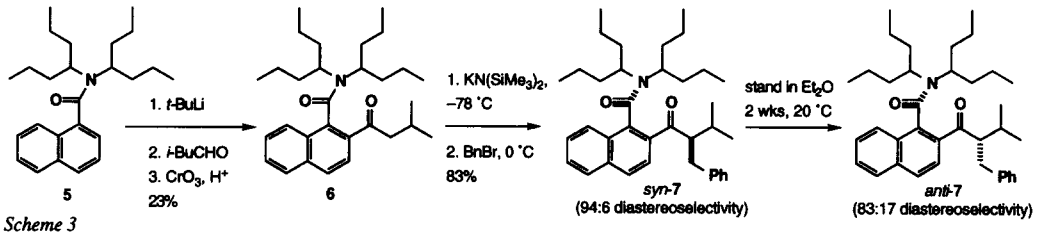
Reducing agents attack the ketones **1** *syn* to the amide carbonyl group, giving high levels of (1,4) stereocontrol.[16] We recently found that alkyllithium and Grignard reagents were even more selective, and gave the tertiary alcohols **2** as a single atropisomer with complete (1,4)-asymmetric induction. Both diastereoisomers **2a** (whose structure was proved by X-ray crystallography: Fig. 1) and **2b** were available by complementary routes (Scheme 1), and were resistant to epimerisation even on heating at 55 °C for 28 h.

A *lack* of stability to epimerisation frustrated our attempts at (1,5)-asymmetric induction using the ketones **1** (Scheme 2). We treated **1b** and **1c** with potassium hexamethyldisilazide[17] and then methyl iodide or benzyl bromide: in both cases mixtures of diastereoisomeric products **3** were obtained which epimerised too fast to be separable into atropisomers. The product ratio remained little changed on standing in ether for several days, and appears to be merely a thermodynamically-controlled equilibrating mixture. Trigonal substituents typically provide poor barriers to bond rotation,[18-20] and **3b** had a barrier to epimerisation in dioxane of only 85 kJ mol^{-1} (corresponding to a half-life at 20 °C of 2 min) compared with the alcohol **4**, whose barrier was 109 kJ mol^{-1} (half-life at 20 °C = 20 days).[21]



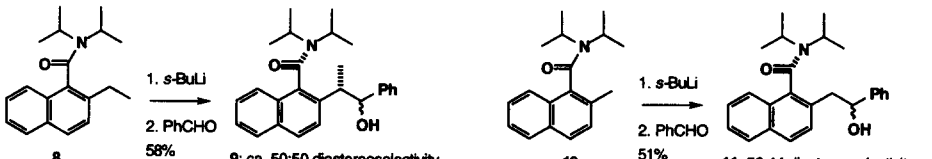
Scheme 2

In an attempt both to improve the thermodynamic stability of the products and to obtain high kinetic selectivity in the enolate alkylation, we made the amide **5** from our bulky "diisoheptyl" amine,[13] and converted it into the ketone **6** by lithiation, addition to isobutyraldehyde[13] and oxidation (Scheme 3).[16] The potassium enolate of this ketone reacted with benzyl bromide to give a 94:6 ratio of atropisomeric diastereoisomers **7** in favour of the *syn* atropisomer shown – an instance of (1,5)-asymmetric induction from the chiral axis to the new stereogenic centre.[10] The selectivity must be kinetic, because the atropisomers could be usefully equilibrated to a reversed 17:83 ratio on standing at 20 °C in ether for 2 weeks.[22,23]

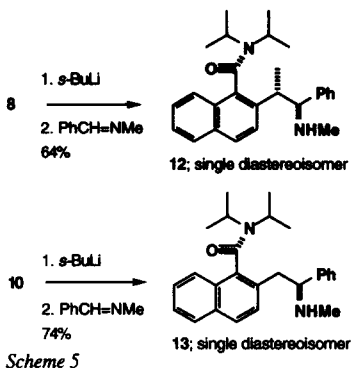


Scheme 3

The most consistently atroposelective reactions we have studied are additions of electrophiles to laterally lithiated[24] amides (diastereoisomeric ratios for [1,4]-asymmetric induction are typically >98:2[14]), so we turned our attention to this class of reaction as a means of controlling (1,5) stereochemistry. We added laterally lithiated **8** to benzaldehyde and got a 1:1 mixture of just two of the four possible diastereoisomers of the alcohol **9** (Scheme 4): there is complete (1,4)- but only poor (1,5)-asymmetric induction. There was a similar lack of (1,5)-stereoselectivity in the addition of laterally lithiated **10** to benzaldehyde to give **11**.



Scheme 4



Scheme 5

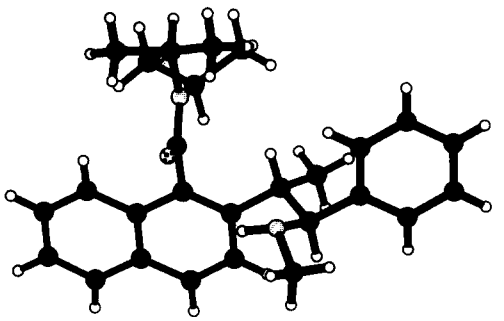
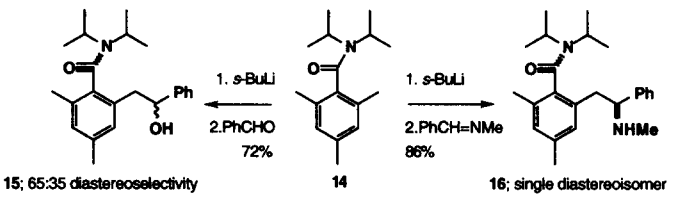


Fig. 2: X-ray crystal structure of **12**

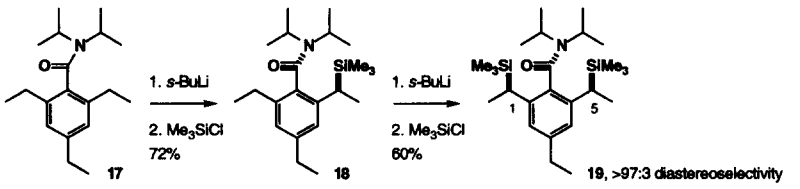
However, with an imine as the electrophile we got *complete selectivity in favour of a single atropisomer* (Scheme 5). Amines **12** and **13** were produced as single diastereoisomers from laterally lithiated **8** and **10**. Fully selective (1,2)-asymmetric induction had been reported previously for the addition of a laterally lithiated amide to an imine,[25] but in the formation of **13** the rotationally restricted amide group exerts control over the formation of a new chiral centre a full 5 atoms away – an instance of complete remote (1,5)-asymmetric induction. The relative stereochemistry of **12** was confirmed by the X-ray crystal structure shown in Fig. 2.

High levels of atroposelectivity are not confined to the reactions of naphthamides,[14] and in order to study remote stereocontrol in the related benzamides we made 2,4,6-trimethylbenzamide **14** from mesitoyl chloride[26] and 2,4,6-triethylbenzamide **17** from triethylbenzene.[27] The trimethylbenzamide **14** reacted much as did the methyl-substituted naphthamide **10**: lithiation and addition to benzaldehyde gave only a 65:35 mixture of atropisomers **15**, while lithiation and addition to N-methylbenzaldimine again gave **16** as a *single atropisomer with complete (1,5)-asymmetric induction* (Scheme 6).



Scheme 6

These benzamides have the potential for atroposelective functionalisation not only at the 2- but also at the 6-position. We wanted to investigate the possibility of using two-directional asymmetric induction to control remote stereogenic centres, so we lithiated **17** and added Me_3SiCl to give **18** as a single diastereoisomer, much as expected given its similarity to naphthamide **8**.[14] Atropisomer **18** could be lithiated again, and a second quench with Me_3SiCl yielded a single atropisomer (>97:3 diastereoselectivity by HPLC) of the 2,4,6-trisubstituted benzamide **19**, now with remote (1,5)-related stereogenic centres (Scheme 7).



Scheme 7

The plane of symmetry of **19** was clearly evident in its NMR spectrum – chiral aromatic *N,N*-diisopropyl amides typically display four distinct 3H doublets in their ^{1}H NMR spectra;[13] that of **19** shows only two 6H doublets for the N*i*-Pr$_2$ group.[28]

Acknowledgements

We are grateful to Madeleine Helliwell (Manchester) for determining the X-ray crystal structure of **2a**, to Chris Frampton (Roche) for determining the X-ray crystal structure of **12**, and to the Leverhulme Trust, the Royal Society and to Zeneca plc (Strategic Research Fund) for research grants.

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17. The enolates of ketones **1** were particularly unreactive: lithium and sodium enolates could not be alkylated, and the potassium enolate reacted only at temperatures over 0 °C
18. Adams, R.; Yuan, H. C. *Chem. Rev.* **1933,** *12*, 261.
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21. The barriers to epimerisation were calculated by following the interconversion of the atropisomers in dioxane solution using HPLC. Full details will be published later.
22. Assignment of relative stereochemistry to *syn*- and *anti*-**7** is tentative: attack of the electrophile on the less hindered face of the Z-enolate (the silyl enol ether obtained from **1c** with KN(SiMe3)$_2$, Me3SiCl is pure Z) would give *syn*-**7**, and molecular modelling (Macromodel–MM2) finds *anti*-**7** to be the lower energy atropisomer.
23. Barriers to epimerisation of diisopropylnaphthamides are typically between 2 and 10 kJ mol^{-1} greater than those of the diethylnaphthamides, with the difference greatest with smaller 2-substituents; we expect this trend to continue with the "diisoheptyl" naphthamides, hence the increased stability of **7** over **3**.
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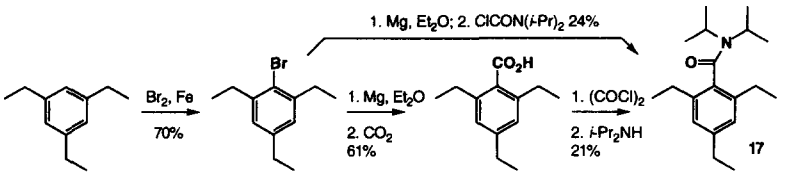
26. The 2,4,6-trimethylbenzamide **14** was made by stirring mesitoyl chloride with excess diisopropylamine.
27. The 2,4,6-triethylbenzamide **17** was made from 1,3,5-triethylbenzene by either of the routes shown below (see Fuson, R. C.; Corse, J. *J. Am. Chem. Soc.*, **1938**, *60*, 2063).



28. The symmetry of the compound tells us only the relative stereochemistry of the 1,5-related stereogenic centres. The stereochemistry of the stereogenic but achirotopic aryl–carbonyl bond is assigned on the basis of work described in reference 14.

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